AMENDMENTS TO THE SPECIFICATION:

Please replace the paragraph beginning at page 2, line 11, with the following amended paragraph (insertions are underlined, deletions are in ~~strikethrough~~):

Genomics has fallen short of the original expectation that this strategy could be used to stratify a population relative to a defined phenotype, including differences between normal and disease patient population or populations. Although single genetic markers have been found to be associated with or cause or predict a specific disease state, genomic information may not be ~~suffieiient~~ sufficient to stratify individual populations by of the association of an SNP (or SNPs) with a given disease, drug side-effect or other target phenotype. Because of the large number of potential targets and regulatory signals that affect protein translation, it is not sufficient to establish the differential expression profiles of messenger RNA in comparing phenotypes or populations, such as healthy and disease states, or such as the analyses using expression DNA chips (*e.g.*, GeneChip™ technology, Affymetrix, Inc., Santa Clara, CA; LifeArray™ technology, Incyte Genomics, Inc., Palo Alto, CA). The metabolic activities in a cell are not performed by mRNA but rather by the translated proteins and subsequently posttranslationally modified products, such as the alkylated, glycosylated and phosphorylated products.

Please replace the paragraph beginning at page 3, line 10, with the following amended paragraph:

Complex protein mixtures are analyzed by two-dimensional (2D) gel electrophoresis and subsequent image processing to identify changes in the pattern (structural changes) or intensity of various protein spots. Two-dimensional ~~dimensionsl~~ gel electrophoresis is a laborious, error-prone method with low reproducibility and cannot be effectively automated. This gel technology is unable to effectively analyze membrane proteins. Further, the resolution of 2D gels is insufficient to analyze the profile of all proteins present in a mixture.

Please replace the paragraph beginning at page 6, line 21, with the following amended paragraph:

Capture compounds, collections of the compounds and methods that use the compounds, singly or in collections thereof, provided herein are designed to capture, separate and analyze

biomolecules, including, but not limited to, mixtures of biomolecules, including biopolymers and macromolecules, individual biomolecules, such as proteins, including individual or membrane proteins. The capture and separation of biomolecules in the methods provided herein, is based on the unique surface features of the biomolecules or mixtures thereof, including but not limited to chemically ~~rective~~ reactive amino acid residues on the surface of a protein or a mixture of proteins. Thus, the capture compounds provided herein are designed not to target any specific biomolecule, but to capture the biomolecules based on the reactive groups present on the surface of the biomolecules or mixtures thereof.

Please replace the paragraph beginning at page 7, line 30, with the following amended paragraph:

A capture compound includes ~~at~~ a chemical reactivity group X (also ~~referrred~~ referred to herein as a function or a functionality), which effects the covalent or a high binding affinity (high k_a) binding, and least one of three other groups (also referred to herein as functions or ~~funtionalities~~ functionalities). The other groups are selected from among a selectivity function Y that modulates the interaction of a biomolecule with the reactivity function, a sorting function Q for addressing the components of the collection, and a solubility function W that alters solubility of the capture compound, such as by increasing the solubility of the capture compound under selected conditions, such as various physiological conditions, including hydrophobic conditions of cell membranes. Hence, for example, if membrane proteins are targeted, then the capture compounds in the collection are designed with solubility functions that increase or provide for solubility in such environment.

Please replace the paragraph beginning at page 11, line 3, with the following amended paragraph:

Also provided herein are methods for the discovery and identification of proteins, which are selected based on a defined phenotype. The methods allow proteins to bind to the target molecules under physiological conditions while maintaining the correct secondary and tertiary conformation of the target. The methods can be performed under physiological and other conditions that permit discovery of ~~bioglogically~~ biologically important proteins, including membrane proteins, that are selected based upon a defined phenotype. Before, during or after exposure of one or a plurality of capture compounds to a mixture of biomolecules, including, but

not limited to, a mixture of proteins, the oligonucleotide portion, or analog thereof, of these compounds is allowed to hybridize to a complementary strand of immobilized oligonucleotide(s), or analog(s) thereof, to allow separation, isolation and subsequent analysis of bound biomolecules, such as proteins, by, for example, mass spectrometry, such as matrix assisted laser desorption ionization-time of flight (MALDI-TOF) mass spectrometry, colorimetric, fluorescent or chemiluminescent tagging, or to allow for increased resolution by mass spectrometry, including MALDI-TOF mass spectrometry.

Please replace the paragraph beginning at page 15, line 14, with the following amended paragraph:

Figure 31 shows selective protein capture using capture compounds. Capture compounds A and B containing sulfonamide interact with Carbonic Anhydrase. (According to literature, its Kd for CA II isoform is ~10nM, and for CA I is ~1 ~~uM~~ <u>μM</u> (both values independently confirmed using activity assay). Using purified proteins, affinity and capture efficiency is highest for Carbonic II, lower for CA I, and negligible for other purified proteins tested.

Please replace the paragraph beginning at page 15, line 22, with the following amended paragraph:

Figure 33 shows isolation of Carbonic Anhydrase from complex protein mixtures using capture compound A. CA II was doped into a FPLC purified protein mixture from the human kidney cell line ~~HEK293,~~ <u>HEK293</u>. The doped CAII was pulled out from all other proteins using avidin-coated (SoftLink) resin. Other proteins were discarded, yielding purified protein ready for further analysis.

Please replace the paragraph beginning at page 15, line 28, with the following amended paragraph:

Figure 34 shows isolation of Carbonic Anhydrase from highly complex protein mixtures using capture compound A. CA II was doped into the whole cytosolic extract from the human kidney cell line ~~HEK293,~~ <u>HEK293</u>. The doped CAII was pulled out from all other proteins using avidin-coated (SoftLink) resin. Other proteins were discarded, yielding purified protein ready for further analysis.

Please replace the paragraph beginning at page 19, line 30, with the following amended paragraph:

As used herein, biomolecule includes biopolymers and macromolecules and all molecules that can be isolated from living organisms and viruses, including, but are not limited to, cells, tissues, prions, animals, plants, viruses, bacteria and other ~~organsims~~ organisms.

Please replace the paragraph beginning at page 22, line 25, with the following amended paragraph:

As used herein, a "mass modification," with respect to a biomolecule to be analyzed for mass spectrometry, refers to the inclusion of changes in ~~consituent~~ constituent atoms or groups that change the molecular weight of the resulting molecule in defined increments detectable by mass spectrometric analysis. Mass modifications do not include radiolabels, such as isotope labels or ~~or fluroescent~~ ~~gropus~~ fluorescent groups or other such tags normally used for detection by means other than mass spectrometry.

Please replace the paragraph beginning at page 24, line 30 with the following amended paragraph:

As used herein, an array refers to a collection of elements, such as the capture compounds, containing three or more members. An addressable array is one in that the members of the array are identifiable, typically by position on a solid phase support but also by virtue of an identifier or detectable label. Hence, in general the members of an array are be immobilized to discrete identifiable loci on the surface of a solid phase. A plurality of ~~of~~ the compounds are attached to a support, such as an array (*i.e.*, a pattern of two or more) on the surface of a support, such as a silicon chip or other surface, generally through binding of the sorting functionality with a group or compound on the surface of the support. Addressing can be achieved by labeling each ~~each~~ member electronically, such as with an radio-frequency (RF) tag, through the use of color coded beads or other such identifiable and color coded labels and through molecular weight. These labels for addressing serve as sorting functions "Q." Hence, in general the members of the array are immobilized to discrete identifiable loci on the surface of a solid phase or directly or indirectly linked to or otherwise associated with the identifiable label, such as affixed to a microsphere or other particulate support (herein referred to as beads) and suspended in solution or spread out on a surface.

Please replace the paragraph beginning at page 35, line 4, with the following amended paragraph:

It is understood that equivalent stringencies can be achieved using alternative buffers, salts and temperatures. By way of example and not limitation, procedures using conditions of low stringency are as follows (see also Shilo and Weinberg, *Proc. Natl. Acad. Sci. USA 78*:67896792 (1981)): Filters containing DNA are pretreated for 6 hours at 40°C in a solution containing 35% formamide, 5X SSC, 50 mM TrisHCl (pH 7.5), 5 mM EDTA, 0.1% PVP, 0.1% Ficoll, 1% BSA, and 500 ~~ìg~~ µg/ml denatured salmon sperm DNA (10X SSC is 1.5 M sodium chloride, and 0.15 M sodium citrate, adjusted to a pH of 7).

Please replace the paragraph beginning at page 35, line 13, with the following amended paragraph:

Hybridizations are carried out in the same solution with the following modifications: 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ~~ìg~~ µg/ml salmon sperm DNA, 10% (wt/vol) dextran sulfate, and 520 X 10^6 cpm ~~^{32}Plabeled~~ ^{32}P-labeled probe is used. Filters are incubated in hybridization mixture for 1820 hours at 40°C, and then washed for 1.5 hours at 55°C in a solution containing 2X SSC, 25 mM TrisHCl (pH 7.4), 5 mM EDTA, and 0.1% SDS. The wash solution is replaced with fresh solution and incubated an additional 1.5 hours at 60°C. Filters are blotted dry and exposed for autoradiography. If necessary, filters are washed for a third time at 6568°C and ~~reexposed~~ re-exposed to film. Other conditions of low stringency which can be used are well known in the art (*e.g.*, as employed for cross-species hybridizations).

Please replace the paragraph beginning at page 35, line 24, with the following amended paragraph:

By way of example and not way of limitation, procedures using conditions of moderate stringency include, for example, but are not limited to, procedures using such conditions of moderate stringency are as follows: filters containing DNA are pretreated for 6 hours at 55°C in a solution containing 6X SSC, 5X Denhart's solution, 0.5% SDS and 100 ~~ìg~~ µg/ml denatured salmon sperm DNA. Hybridizations are carried out in the same solution and 520 X 10^6 cpm ~~^{32}Plabeled~~ ^{32}P-labeled probe is used. Filters are incubated in hybridization mixture for 18-20 hours at 55°C, and then washed twice for 30 minutes at 60°C in a solution containing 1X SSC

and 0.1% SDS. Filters are blotted dry and exposed for autoradiography. Other conditions of moderate stringency which can be used are well-known in the art. Washing of filters is done at 37°C for 1 hour in a solution containing 2X SSC, 0.1% SDS.

Please replace the paragraph beginning at page 36, line 5, with the following amended paragraph:

By way of example and not way of limitation, procedures using conditions of high stringency are as follows: Prehybridization of filters containing DNA is carried out for 8 hours to overnight at 65°C in buffer composed of 6X SSC, 50mM TrisHCl (pH 7.5), 1 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.02% BSA, and 500 ~~ìg~~ μg/ml denatured salmon sperm DNA. Filters are hybridized for 48 hours at 65°C in prehybridization mixture containing 100 ~~ìg~~ μg/ml denatured salmon sperm DNA and 520 X 10^6 cpm of ~~^{32}Plabeled~~ ^{32}P-labeled probe. Washing of filters is done at 37°C for 1hour in a solution containing 2X SSC, 0.01% PVP, 0.01% Ficoll, and 0.01% BSA. This is followed by a wash in 0.1X SSC at 50°C for 45 minutes before autoradiography. Other conditions of high stringency which can be used are well known in the art.

Please replace the paragraph beginning at page 45, line 9, with the following amended paragraph:

As used herein, the term "amino acid" refers to ~~á-amino~~ α-amino acids that are racemic, or of either the D- or L-configuration. The designation "d" preceding an amino acid designation (*e.g.*, dAla, dSer, dVal, etc.) refers to the D-isomer of the amino acid. The designation "dl" preceding an amino acid designation (*e.g.*, dlAla) refers to a mixture of the L- and D-isomers of the amino acid.

Please replace the paragraph beginning at page 47, line 2, with the following amended paragraph:

As shown in Figure 27, the selectivity function interacts via non-covalent interactions with a protein e.g. in the active site of enzymes or ligand binding site of receptors ("Biased approach" for e.g. non-target identification), or at a surface affinity motif (SAM) outside of the binding site ("Unbiased approach" for e.g. target discovery). A biased selectivity group enables isolation of specific proteins from complex mixtures. In one embodiment, the selectivity function is a drug (or metabolite thereof) known to cause side effects, attached in several

different orientations to make different parts of the molecule accessible to proteins. An unbiased selectivity function utilizes chemical features underlying affinity interactions with the protein surface. The unbiased selectivity function tends to be less specific than the biased, since it is designed to interact with a ~~a~~ broader set of proteins. Use of the unbiased capture compounds to screen for global protein profile differences between healthy and disease cells would require the development of a library of capture compounds which as a set interact with the majority of the proteins in the proteome. This approach enables monitoring of protein profile differences induced by the influence of a drug molecule, or discovering new potential drug targets or biomarkers based on the differences between healthy with disease cells.

Please replace the paragraph beginning at page 47, line 21, with the following amended paragraph:

In one embodiment, the reactivity function covalently "captures" or binds to the selected protein. While the selectivity function serves as the bait, the reactivity function serves as the hook. A protein thus captured will be able to survive downstream purification and analytical processes. Reactivity functions employed are chemically reactive with certain protein side chains (e.g. NHS forms bond with lysine amino function), or require an activation step (~~i.e.light~~ i.e., light) prior to forming covalent bond (e.g. photoactivated moiety such as azide which forms a nitrene radical).

Please replace the paragraph beginning at page 50, line 20, with the following amended paragraph:

The capture compounds that include functional groups that confer reactivity, selective and separative properties, depending on the specificity of separation and analysis required (which depends on the complexity of the mixture to be analyzed). As more functional groups are added to the compounds, the compounds can exhibit increased selectivity and develop a signature for target molecules similar to an antigen (Ag) binding site on an antibody. In general, the compounds provided herein include at least two functional groups (functions) selected from four types of functions: a reactivity function, which binds to biopolymers either covalently or with a high k_a (generally greater than about 10^9, 10^{10}, 10^{12} liters/mole and/or such that the binding is substantially irreversible or stable under conditions of mass spectrometric analyses, such as MALDI-MS conditions); a selectivity function, which by virtue of non-covalent

interactions alters, generally increases, the specificity of the reactivity function; a sorting function, which permits the compounds to be addressed (arrayed or otherwise separated based according to the structure of the capture compound; and a solubility function, which when selected alters the solubility of the compounds depending upon the environment in which reactions are performed, permitting the conditions to simulate physiological conditions. In general, the reactivity function is the reactive group that specifically interacts, typically covalently or with high binding affinity (k_a), with particular biomolecules, such as proteins, or portions thereof; and the other functionality, the selectivity functions, alters, typically increasing, the specificity of the reactivity function. In general, the reactive function covalently interacts with groups on a particular biomolecule, such as amine groups on the surface of a protein. The reactivity function interacts with biomolecules to form a covalent bond or a non-covalent bond that is stable under conditions of analysis, generally with a k_a of greater than 10^9 liters/mole or greater than 10^{10} liters/mole. Conditions of analysis include, but are not limited to, mass spectrophotometric analysis, such as matrix assisted laser desorption ionization-time of flight (MALDI-TOF) mass spectrometry. The selectivity function influences the types of biomolecules that can interact with the reactivity function through a non-covalent interaction. The selectivity function alters the specificity for the particular groups, generally reducing the number of such groups with which the reactivity functions react. A goal is to reduce the ~~the~~ number of proteins or biomolecules bound at a locus, so that the proteins can then be separated, such as by mass spectrometry.

Please replace the paragraph beginning at page 51, line 25, with the following amended paragraph:

Included among the capture compounds provided herein are those that ~~can , the compounds for use in the methods herein~~ can be classified in at least two sets: one for reactions in aqueous solution (*e.g.*, for reaction with hydrophilic biomolecules), and the other for reaction in organic solvents (*e.g.*, chloroform)(*e.g.*, for reaction with hydrophobic biomolecules). Thus, in certain embodiments, the compounds provided herein discriminate between hydrophilic and hydrophobic biomolecules, including, but not limited to, proteins, and allow for analysis of both classes of biomolecules.

Please replace the paragraph beginning at page 52, line 17, with the following amended paragraph:

X, the reactivity functionality, is selected to be anything that forms such a covalent bond or a bond of high affinity that is stable under conditions of mass spectrometric analysis, particularly MALDI analysis. The selectivity functionality Y, is a group that "looks" at the topology of the protein around reactivity binding sites and functions to select particular groups on ~~biolmolecules~~ biomolecules from among those with which a reactivity group can form a covalent bond (or high affinity bond). For example, a selectivity group can cause steric hindrance, or permit specific binding to an epitope, or anything in between. It can be a substrate for a drug, lipid, peptide. It selects the environment of the groups with which the reactivity function interacts. The selectivity functionality Y, can be one whereby a capture compound forms a covalent bond with a biomolecule in a mixture or interacts with high stability such that the affinity of binding of the capture compound to the biomolecule through the reactive functionality in the presence of the selectivity functionality is at least ten-fold or 100-fold greater than in the absence of the selectivity functionality.

Please replace the paragraph beginning at page 53, line 2, with the following amended paragraph:

Q is a sorting function that can be anything that provides a means for separating each set of capture compounds from the others, such as by arraying, and includes, groups such as biotin, generally a spacer, binding to an avidin on a surface (or vice versa) array, oligonucleotides for binding oligonucleotide arrays or any molecule that has a cognate binding partner to which it binds with sufficient ~~affinitity~~ affinity to survive mass spectrometric analysis, such as MALDI-MS analysis, can be selected. For any collection a variety of different sorting groups can be used; each set of capture compounds should have unique Q compared to the other sets. In addition, labeling means that can be sorted by virtue of the label, such as RF tags, ~~fluroescent~~ fluorescent tags, color-coded tags or beads, bar-coded or other symbology labeled tags and other such labels can be used. For example, the capture compounds or the X, Y, Z, W functionalities can be on a surface that is attached to an RF tag or a colored tag. These can be readily sorted after reaction so that each set can be separately analyzed to identify bound biomolecules. Thus, the collections can include capture compounds that have a variety of sorting groups.

Please replace the paragraph beginning at page 54, line 11 with the following amended paragraph:

In certain embodiments, Z is a trifunctional ~~moities~~ moieties containing three functionalities that are each capable of being derivatized selectively in the presence of the other two functionalities. Non-limiting examples of such trifunctional moieties include but are not limited to trifunctionalized trityl groups and amino acids that possess a functionality on the side chain (e.g., tyrosine, cysteine, aspartic acid, glutamic acid, lysine, threonine, serine, etc.). Such amino acids include natural and non-natural amino acids.

Please replace the paragraph beginning at page 55, line 9 with the following amended paragraph:

In some embodiments, a lipid bilayer, such as ~~as~~ those used for forming liposomes and other micelles, can be provided on the surface of a support as a way of maintaining the structures of membrane proteins to make a lipid bilayer on the surface. This can be employed where the support is the "Z" function and the other functions are linked thereto, or where the compounds are linked to a support through a Q group, such as by double-stranded oligonucleotides. The resulting immobilized capture compounds can be coated with or dissolved in a lipid coating. As a result, the compounds and collections provided herein can act as an artificial membrane, dendrimer polymer chemistry can be employed for controlled synthesis of membranes having consistent pore dimensions and membrane thicknesses, through synthesis of amphiphilic dendrimeric or hyperbranched block copolymers that can be self-assembled to form ultrathin organic film membranes on porous supports. In one embodiment, an organic film membrane is composed of a linear-dendritic diblock copolymer composed of polyamidoamine (PAMAM) dendrimer attached to one end of a linear polyethylene oxide (PEO) block.

Please replace the paragraph beginning at page 62, line 9 with the following amended paragraph:

straight or ~~brached~~ branched chain alkyl, straight or branched chain alkenyl, straight or branched chain alkynyl, aryl, heteroaryl, cycloalkyl, heterocyclyl, straight or branched chain aralkyl, straight or branched chain aralkenyl, straight or branched chain aralkynyl, straight or branched chain heteroaralkyl, straight or branched chain heteroaralkenyl, straight or branched chain heteroaralkynyl, straight or branched chain cycloalkylalkyl, straight or branched chain

cycloalkylalkenyl, straight or branched chain cycloalkylalkynyl, straight or branched chain heterocyclylalkyl, straight or branched chain heterocyclylalkenyl or straight or branched chain heterocyclylalkynyl.

Please replace the paragraph beginning at page 63, line 16 with the following amended paragraph:

For some embodiments, for example, where the biomolecule and the sorting function possess low steric ~~hinderance~~ hindrance, a spacer is optional. In certain embodiments, steric hindrance also can enhance selectivity in conjunction with Y (or in the absence of a Y). This enhanced selectivity can be achieved either by the presence of a selectivity function, Y, that is attached to M or by the selection of the appropriate spacer molecules for S^1 and/or S^2. In other embodiments, the spacer group is selected such that the selectivity ~~fuction~~ function (e.g. a drug) reaches the binding pocket of a target or non-target protein. Spacer groups may be hydrophobic (e.g. PEGs or phosphodiesters) or hydrophilic; their length may be varied to achieve efficient sorting or selectivity or capture; they may be rigid (e.g. trans olefins). The spacer groups may be selected based on the properties (hydrophobic/hydrophilic, size, etc.) of the biomolecular mixture to be analyzed.

Please replace the paragraph beginning at page 64, line 19, with the following amended paragraph:

In certain embodiments, R^{15} is H, OH, OR^{51}, SH, SR^{51}, NH_2, NHR^{51}, $NR^{51}{}_2$, F, Cl, Br, I, SO_3H, $\cancel{PO}^2{}_4$ PO_4, CH_3, CH_2CH_3, $CH(CH_3)_2$ or $C(CH_3)_3$; where R^{51} is straight or branched chain alkyl, straight or branched chain alkenyl, straight or branched chain alkynyl, aryl, heteroaryl, cycloalkyl, heterocyclyl, straight or branched chain aralkyl, straight or branched chain aralkenyl, straight or branched chain aralkynyl, straight or branched chain heteroaralkyl, straight or branched chain heteroaralkenyl, straight or branched chain heteroaralkynyl, straight or branched chain cycloalkylalkyl, straight or branched chain cycloalkylalkenyl, straight or branched chain cycloalkylalkynyl, straight or branched chain heterocyclylalkyl, straight or branched chain heterocyclylalkenyl or straight or branched chain heterocyclylalkynyl.

Please replace the paragraph beginning at page 65, line 12, with the following amended paragraph:

In certain embodiments, the cleavable group L is cleaved either prior to or during analysis of the biomolecule, such as a protein . The analysis can include mass spectral analysis, for example MALDI-TOF mass spectral analysis. The cleavable group L is selected so that the group is stable during conjugation to a biomolecule, and sorting, such as hybridization of a single stranded oligonucleotide Q moiety to a complementary sequence, and washing of the hybrid; but is ~~susceptable~~ susceptible to cleavage under conditions of analysis of the biomolecule, including, but not limited to, mass spectral analysis, for example MALDI-TOF analysis. In certain embodiments, the cleavable group L can be a disulfide moiety, created by reaction of the compounds where X = SH, with the thiol side chain of cysteine residues on the surface of biomolecules, including, but not limited to, proteins. The resulting disulfide bond can be cleaved under various reducing conditions including, but not limited to, treatment with dithiothreitol and 2-mercaptoethanol.

Please replace the paragraph beginning at page 69, line 3, with the following amended paragraph:

where R^{15}, R^{51} and y are as defined above. In certain embodiments, R^{15} is H, OH, OR^{51}, SH, SR^{51}, NH_2, NHR^{51}, $N(R^{51})_2$, F, Cl, Br, I, SO_3H, $\cancel{PO}^{2}{}_{4}$ PO_4, CH_3, CH_2CH_3, $CH(CH_3)_2$ or $C(CH_3)_3$; where R^{51} is straight or branched chain alkyl, straight or branched chain alkenyl, straight or branched chain alkynyl, aryl, heteroaryl, cycloalkyl, heterocyclyl, straight or branched chain aralkyl, straight or branched chain aralkenyl, straight or branched chain aralkynyl, straight or branched chain heteroaralkyl, straight or branched chain heteroaralkenyl, straight or branched chain heteroaralkynyl, straight or branched chain cycloalkylalkyl, straight or branched chain cycloalkylalkenyl, straight or branched chain cycloalkylalkynyl, straight or branched chain heterocyclylalkyl, straight or branched chain heterocyclylalkenyl or straight or branched chain heterocyclylalkynyl.

Please replace the paragraph beginning at page 71, line 15, with the following amended paragraph:

In other embodiments, Z can be an insoluble support or a substrate, such as a particulate solid support, such as a silicon or other "bead" or microsphere, or solid surface so that the surface

presents the functional groups (X, Y, Q and, as needed W). In these embodiments, Z has bound to it one or a plurality of X moieties (typically, 1 to 100, generally 1 to 10) and optionally to at least one Q and/or Y moiety, and also optionally to one or more W moieties. Z, in these embodiments, can have tens up to hundreds, thousands, millions, or more functional moieties (groups) on its surface. For example, the capture compound can be a silicon ~~particule~~ particle or a agarose or other ~~paricle~~ particle with groups presented on it. As discussed below, it further can be coated with a hydrophobic material, such as lipid bilayers or other lipids that are used, for example to produce liposomes. In such embodiments, the resulting particles with a hydrophobic surface and optional hydrophobic W groups are used in methods for probing cell membrane environments and other intracellular environments. Gentle lysis of cells, can expose the intracellular compartments and organelles, and hydrophobic capture compounds, such as these, can be reacted with them, and the bound biomolecules assessed by, for example, mass spectrometry or further treated to release the contents of the compartments and organelles and reacted with the capture compounds or other capture compounds.

Please replace the paragraph beginning at page 74, line 21 with the following amended paragraph:

and R^{10} is a divalent group including $(CH_2CH_2O)_zCH_2CH_2O$, $(CH_2CH_2O)_zCH_2CH_2O$alkylene, alkylene, alkenylene, alkynylene, arylene, heteroarylene, $(CH_2)_zCH_2O$, $(CH_2)_zCH_2O$alkylene, $(CH_2CH_2NH)_zCH_2CH_2NH$, $CH_2CH(OH)CH_2O$, $Si(R^{12})(R^{13})$, CHF and CF_2; where y is an integer from 1 to 20; z is an integer from 0 to 200; R^{11} is the side chain of an ~~á-amino~~ α-amino acid; and R^{12} and R^{13} are each independently selected from alkyl, aryl and aralkyl.

Please replace the paragraph beginning at page 75, line 11, with the following amended paragraph:

Other mass modifying tags include, but are not limited to CHF, CF_2, $Si(CH_3)_2$, $Si(CH_3)(C_2H_5)$ and $Si(C_2H_5)_2$. In other embodiments, the mass modifying tags include homo- or heteropeptides. A non-limiting example that generates mass-modified species with a mass increment of 57 is an oligoglycine, which produce mass modifications of, *e.g.*, 74 (y = 1, z = O), 131 (y = 1, z = 2), 188 (y = 1, z = 3) or 245 (y = 1, z = 4). Oligoamides also can be used, *e.g.*, mass-modifications of 74 (y = 1, z = 0), 88 (y = 2, z = 0), 102 (y = 3, z = 0), 116 (y = 4, z = 0), etc., are obtainable. Those skilled in the art will appreciate that there are numerous possibilities

in addition to those ~~exemplefied~~ exemplified herein for introducing, in a predetermined manner, many different mass modifying tags to the compounds provided herein.

Please replace the paragraph beginning at page 76, line 16 with the following amended paragraph:

Thus, for example, X is a group that reacts or interacts with functionalities on the surface of a protein to form covalent or non-covalent bonds with high affinity. A wide selection of different functional groups are available for X to interact with a protein. For example, X can act either as a nucleophile or an electrophile to form covalent bonds upon reaction with the amino acid residues on the surface of a protein. Exemplary reagents that bind covalently to amino acid side chains include, but are not limited to, protecting groups for hydroxyl, carboxyl, amino, amide, and thiol moieties, including, for example, those disclosed in T.W. Greene and P.G.M. Wuts, "Protective Groups in Organic Synthesis," 3rd ed. (1999, Wiley Interscience); photoreactive groups, Diels Alder couples (*i.e.*, a diene on one side and a ~~sngle~~ single double bond on the other side).

Please replace the paragraph beginning at page 88, line 17, with the following amended paragraph:

The selectivity functions ("Y") serves to modulate the reactivity function by reducing the number of groups to which the reactivity functions bind, such as by steric hindrance and other interactions. It is a group that modifies the steric and/or electronic (*e.g.*, mesomeric, inductive effects) properties as well as the resulting affinities of the capture compound. Selectivity functions include any functional groups that increase the selectivity of the reactivity group so that it binds to fewer different biomolecules than in the absence of the selectivity function or binds with greater affinity to ~~biolmolecules~~ biomolecules than in its absence. In the capture compounds provided herein, Y is allowed to be extensively varied depending on the goal to be achieved regarding steric hindrance and electronic factors as they relate to modulating the reactivity of the cleavable bond L, if present, and the reactive functionality X. For example, a reactivity function X can be selected to bind to amine groups on proteins; the selectivity function can be selected to ensure that only groups exposed on the surface can be accessed. The selectivity function is such that the compounds bind to or react with (via the reactivity function) fewer different biomolecules when it is part of the molecule than when it is absent and/or the

compounds bind with greater specificity and higher affinity The selectivity function can be attached directly to a compound or can be attached via a linker, such as CH_2CO_2 or CH_2-O-$(CH_2)_n$-O, where n is an integer from 1 to 12, or 1 to 6, or 2 to 4. See, *e.g.*, Figure 17 and Figure 21 and the discussion below for exemplary selectivity functions. In certain embodiments, the linker is chosen such that the selectivity function can reach the binding pocket of a target or non-target protein.

Please replace the paragraph beginning at page 89, line 10, with the following amended paragraph:

In certain embodiments, each Y is independently a group that modifies the affinity properties ~~properites~~ and/or steric and/or electronic (*e.g.*, mesomeric, inductive effects) properties of the resulting capture compound. For example, Y, in certain embodiments, is selected from ATP analogs and inhibitors; peptides and peptide analogs; polyethyleneglycol (PEG); activated esters of amino acids, isolated or within a peptide; cytochrome C; and hydrophilic trityl groups.

Please replace the paragraph beginning at page 90, line 2, with the following amended paragraph:

In certain embodiments the selectivity function is selected from pharmaceutical drugs or drug fragments set forth below, where attachment of exemplary pharmaceutical drugs to a ~~cental~~ central core is shown below. In other embodiments, the selectivity function is a drug, drug fragment, drug metabolite, or a drug synthetic intermediate.

Please replace the paragraph beginning at page 99, line 29, with the following amended paragraph:

Chemiluminescent groups intended for use herein include any components of light generating systems that are catalyzed by a peroxidase and require superoxide anion (O) (and/or hydrogen peroxide (H_2O_2))(see, *e.g.*, Musiani *et al.* (1998) *Histol. Histopathol. 13(1)*:243-8). ~~Lightgenerating~~ Light generating systems include, but are not limited to, luminol, isoluminol, peroxyoxalate-fluorophore, acridinium ester, lucigenin, dioxetanes, oxalate esters, acridan, hemin, indoxyl esters including 3-*O*-indoxyl esters, naphthalene derivatives, such as 7-dimethyl-amino-naphthalene-1,2-dicarbonic acid hydrazide and cypridina luciferin analogs, including 2-methyl-6-[p-methoxyphenyl]-3,7-dihyroimidazo[1,2-~~á~~ α]pyrazin-3-one, 2methyl-6-phenyl-3,7-

dihyroimidazo[1,2-~~á~~ α]pyrazin-3-one and 2-methyl-6-[p-[2-[sodium 3-carboxylato-4-(6-hydroxy-3-xanthenon-9-yl]phenylthioureylene]ethyleneoxy]phenyl]-3,7-dihyroimidazo[1,2-α]pyrazin-3-one. In other embodiments, the chemiluminescent moieties intended for use herein include, but are not limited to, luminol, isoluminol, N-(4-aminobutyl)-N-ethyl isoluminol (ABEI), N-(4-aminobutyl)-N-methyl isoluminol (ABMI), which have the following structures and participate in the following reactions:

Please replace the paragraph beginning at page 101, line 24, with the following amended paragraph:

~~Examplary~~ Exemplary selectivity functions include, but are not limited to, ligands that bind to receptors such as insulin and other receptors (see, *e.g.*, the Table of ligands below); cyclodextrins; enzyme substrates; lipid structures; prostaglandins; antibiotics; steroids; therapeutic drugs; enzyme inhibitors; transition state analogs; specific peptides that bind to biomolecule surfaces, including glue peptides; lectins (*e.g.*, mannose type, lactose type); peptide mimetics; statins; functionalities, such as dyes and other compounds and moieties employed for protein purification and affinity ~~chromatraphy~~ chromatography. See *e.g.*, Figure 17, and the following table of peptide ligands:

Please replace the paragraph beginning at page 108, line 24 with the following amended paragraph:

Other sorting ~~fuctions~~ functions for use in the compounds provided herein include biotin, $(His)_6$, BODIPY (4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene), oligonucleotides, nucleosides, nucleotides, antibodies, immunotoxin conjugates, adhesive peptides, lectins, liposomes, PNA (peptide nucleic acid), activated dextrans and peptides. In one embodiment, the sorting function is an oligonucleotide, particularly, either a single-stranded or partially single-~~stranted~~ stranded oligonucleotide to permit hybridization to single-stranded regions on complementary oligonucleotides on solid supports.

Please replace the paragraph beginning at page 110, line 13, with the following amended paragraph:

In certain embodiments, Q is a monovalent oligonucleotide or oligonucleotide analog group that is at least partially single stranded or includes a region that can be single-stranded for hybridization to complementary oligonucleotides on a ~~a~~ support. Q can have the formula:

$N^1{}_m B_i N^2{}_n$

where N^1 and N^2 are regions of conserved sequences; B is a region of sequence permutations; m, i and n are the number of building blocks in N^1, B and N^2, respectively; and the sum of m, n and i is a number of units able to hybridize with a complementary nucleic acid sequence to form a stable hybrid. Thus, in embodiments where B is a single stranded DNA or RNA, the number of sequence permutations is equal to 4^i. In one embodiment, the sum of m, n and i is about 5 up to about 10, 15, 25, 30, 35, 40, 45 or 50. In certain embodiments m and n are each independently 0 to about 48, or are each independently about 1 to about 25, or about 1 to about 10 or 15, or about 1 to about 5. In other embodiments, i is about 2 to about 25, or is about 3 to about 12, or is about 3 to about 5, 6, 7 or 8.

Please replace the paragraph beginning at page 112, line 3, with the following amended paragraph:

The compounds provided herein can ~~incude~~ include a solubility function, W, to confer desired solubility properties, such as solubility in hydrophobic environments or hydrophilic environments to permit probing of biomolecules in physiological environments, such as in membranes. Exemplary solubility functions for use in the compounds provided herein include polyethylene glycols, sulfates, polysulfates, phosphates, sulfonates, polysulfonates, carbohydrates, dextrin, polyphosphates, poly-carboxylic acids, triethanolamine, alcohols, water soluble polymers, salts of alkyl and aryl carboxylic acids and glycols.

Please replace the paragraph beginning at page 114, line 14, with the following amended paragraph:

where Q is a sorting function that is a compound, or one or more biomolecules (*e.g.*, a pharmaceutical drug preparation, a biomolecule, drug or other compound that immobilizes to the substrate and captures target biomolecules), which is(are) capable of specific noncovalent binding to a known compound to produce a ~~tighly~~ tightly bound capture compound;

Please replace the paragraph beginning at page 124, line 9, with the following amended paragraph:

The capture compounds are designed by assessing the target biomolecules and reaction conditions. For example, if the target biomolecules are proteins, X functions suitable to effect

covalent or binding to proteins with high affinity are selected. Y is selected according to the complexity of the target mixture and the desired specificity of binding by X. Q is selected according the number of divisions of the mixture that are desired; and W is selected based upon the environment of the ~~biolmolecules~~ biomolecules that is probed. A variety of capture compounds are designed according to such criteria.

Please replace the paragraph beginning at page 133, line 19, with the following amended paragraph:

As noted, an array encompasses not only 2-D arrays on solid supports but any collection that is addressable or in which members are identifiable, such as by tagging with colored beads or RF tags or chemical tags or symbologies on beads. "Spots" are loci on the array, collections where capture compounds are sorted ~~acccoding~~ according to their "Q" function are separated.

Please replace the paragraph beginning at page 136, line 27, with the following amended paragraph:

In MALDI mass spectrometry (MALDI-MS), various mass analyzers can be used, *e.g.*, magnetic sector/magnetic deflection instruments in single or triple quadrupole mode (MS/MS), Fourier transform and ~~timeofflight~~ time-of-flight (TOF), including orthogonal time-of-flight (O-TOF), configurations as is known in the art of mass spectrometry. For the desorption/ionization process, numerous matrix/laser combinations can be used. ~~Iontrap~~ Ion trap and reflectron configurations also can be employed.

Please replace the paragraph beginning at page 138, line 6, with the following amended paragraph:

In the above embodiments, including those where Z contains a cleavable linkage, the compounds can contain a mass modifying tag. In these embodiments, the mass modifying tag is used to analyze the differences in structure (*e.g.*, side chain modification such as ~~phosphoylation~~ phosphorylation or dephosphorylation) and/or expression levels of biomolecules, including proteins. In one embodiment, two compounds (or two sets of compounds having identical permuted B moieties) are used that only differ in the presence or absence of a mass modifying tag (or have two mass tags with appropriate mass differences). One compound (or one set of compounds) is (are) reacted with "healthy" tissue and the mass modified compound(s) are

reacted with the "disease" tissue under otherwise identical conditions. The two reactions are pooled and analyzed in a duplex mode. The mass differences will elucidate those proteins that are altered structurally or expressed in different quantity in the disease tissue. Three or more mass modifying tags can be used in separate reactions and pooled for multiplex analysis to follow the differences during different stages of disease development (*i.e.*, mass modifying tag 1 at time point 1, mass modifying tag 2 at time point 2 etc.), or, alternatively, to analyze different tissue sections of a disease tissue such as a tumor sample.

Please replace the paragraph beginning at page 138, line 25 with the following amended paragraph:

Selectivity in the reaction of the compounds provided herein with a biomolecule, such as a protein mixture also can be achieved by performing the reactions under kinetic control and by withdrawing aliquots at different time intervals. Alternatively, different parallel reactions can be performed (for example, all differing in the B moiety of the Q group) and either performed with different ~~stochiometric~~ stoichiometric ratios or stopped at different time intervals and analyzed separately.

Please replace the paragraph beginning at page 139, line 10 with the following amended paragraph:

In other embodiments, the methods are performed by tagging the biomolecules to be analyzed, including but not limited to proteins, with more than one, in one embodiment three to five, of the compounds provided herein. Such compounds possess functionality designed to target smaller chemical features of the biomolecules rather than a macromolecular feature. See, *e.g.*, Figure 3. Such smaller chemical features include, but are not ~~limted~~ limited to, NH_2, SH, SS (after capping SH, SS can be targeted by, *e.g.*, gold), and OH. In one non-limiting example, the phenolic OH of tyrosine is selectively captured using a diazo compound, such as an aryldiazonium salt. In this embodiment, the reaction can be performed in water. For example, a functionalized diazonium salt could be used where the functionality allows for subsequent capture of a compound provided herein, thereby providing a oligonucleotide-labelled biomolecule. One such functionalized diazonium salt is:

Please replace the paragraph beginning at page 140, line 12, with the following amended paragraph:

In embodiments where the compounds for use in the methods provided herein are insoluble or poorly soluble in water or aqueous buffers, organic solvents are added to the buffers to improve solubility. In one embodiment, the ratio of buffer:organic solvent is such that denaturation of the biomolecule does not occur. In another embodiment, the organic solvents used include, but are not limited to, acetonitrile, formamide and pyridine. In another embodiment, the ratio of buffer:organic solvent is about 4:1. To determine if an organic co-solvent is needed, the rate of reaction of the compounds provided herein with a water-soluble ~~souble~~ amine, such as 5'-aminothymidine, is measured. For example, the following reaction is performed is a variety of solvent mixtures well known to those of skill in the art to determine optimal conditions for subsequent biomolecule tagging and analysis:

Please replace the paragraph beginning at page 145, line 27, with the following amended paragraph:

Immunofluorescence involves the staining of cells with antibodies conjugated to fluorescent dyes such as FITC (fluorescein), PE (phycoerythrin), APC (allophycocyanin), and PE-based tandem conjugates (R670, CyChrome and ~~others.)~~ others). Cell surface antigens are the usual targets of this assay, but antibodies can be directed at antigens or cytokines in the cytoplasm as well.

Please replace the paragraph beginning at page 147, line 9 with the following amended paragraph:

Cell cycles can be synchronized or frozen by a variety of methods, including but are not limited to, cell chelation of critical ions, such as by removal of magnesium, zinc, manganese, ~~cobal~~ cobalt and/or other ions that perform specific functions by EDTA or ~~otherchelators~~ other chelators (see, *e.g.*, EXAMPLES). Other methods include controlling various metabolic or biochemical pathways. Figure 18 depicts exemplary points of regulation of metabolic control mechanisms for cell synchronization. Examples of synchronizing or "freezing" Metabolic Control for synchronizing cells, include, but are not limited to, the following:

Please replace the paragraph beginning at page 149, line 6, with the following amended paragraph:

Also, as discussed above, capture compounds can be designed, such as by appropriate selection of W, to interact with intact organelles before disrupting them in cells that have been gently lysed or otherwise treated to permit access to organelles and internal membranes. Then the captured organelles can be disrupted, such as one which can ~~inelude~~ include an artificial membrane, such as a lipid bilayer or micelle coating, to capture the organelle proteins and other biomolecules in an environment that retains their three-dimensional structure. These captured proteins can be analyzed. This permits the capture compounds to interact with the captured proteins and other biomolecules in their native tertiary structure.

Please replace the paragraph beginning at page 151, line 11 with the following amended paragraph:

For example, protein-protein or protein-biomolecule interactions are exposed to test compounds, typically small molecules, including small organic molecules, peptides, peptide mimetics, antisense molecules or dsRNA, antibodies, fragments of antibodies, recombinant and ~~sythetic~~ synthetic antibodies and fragments thereof and other such compounds that can serve as drug candidates or lead compounds. Bound small molecules are identified by mass spectrometry or other analytical methods.

Please replace the paragraph beginning at page 152, line 30 with the following amended paragraph:

In one embodiment, the capture compounds/collections thereof are designed to contain pharmaceutical drugs/drug fragments, drug metabolites or prodrugs as the selectivity function and suitable reactivity and sorting functionality. In the methods provided herein, the capture compound/collections thereof are allowed to interact with a mixture of drug target and non-target biomolecules, including but not limited to, receptor proteins. The captured biomolecules are then analyzed to identify drug target and non-target biomolecules. Screening and identification of drug non-target biomolecules can help in understanding side effects of the pharmaceutical drugs and permit modification of the drug structure to eliminate or minimize the side effects while maintaining the efficacy. Exemplary drug molecules that can be used in the methods and collections provided herein are set forth elsewhere herein, and include, but are not limited

~~to,.LIPITOR®~~ to, LIPITOR® (atorvastatin calcium), CELEBREX® (celecoxib), VIOXX® (refecoxib) and BAYCOL® (cerivastatin sodium).

Please replace the paragraph beginning at page 157, line 16, with the following amended paragraph:

The systems include the collections provided herein, optionally arrays of such collections, software for control of the processes of sample preparation and instrumental ~~analyis~~ analysis and for analysis of the resulting data, and instrumentation, such as a mass spectrometer, for analysis of the ~~biolmolecules~~ biomolecules. The systems include other devices, such as a liquid chromatographic devices so that a protein mixture is at least partially separated. The eluate is collected in a continuous series of aliquots into, *e.g.*, microtiter plates, and each aliquot reacted with a capture compound provided. In multiplex reactions, aliquots in each well can simultaneously react with one or more of the capture compounds provided herein that, for example each differ in X (*i.e.*, amino, thiol, lectin specific functionality) with each having a specific and differentiating selectivity moiety Y and in the Q group. Chromatography can be done in aqueous or in organic medium. The resulting reaction mixtures are pooled and analyzed directly. Alternatively, subsequent secondary reactions or molecular interaction studies are performed prior to analysis, including mass spectrometric analysis.

Please replace the paragraph beginning at page 158, line 24, with the following amended paragraph:

3) Reaction with Proteome Reagents. Each MTP in turn is transferred to a Proteome Reagent Station harboring 1, 2...m reagents differing only in the oligonucleotide sequence part (*i.e.*, Q) or/and in the chemical nature of the functionality reacting with the proteins (*i.e.*, X). If there are more than one MTP coming from one tissue sample then reagent 1 is added to the same well of the respective MTPs 1, 2...n, *i.e.*, in well A1, reagent 2 in well A2, etc. In embodiments where the MTPs have 96 wells (i = 1-96), 96 different Proteome Reagents (*i.e.*, 96 different compounds provided ~~herien~~ herein, m = 1-96) are supplied through 96 different nozzles from the Proteome Reagent Station to prevent cross-contamination.

Please replace the paragraph beginning at page 169, line 19, with the following amended paragraph:

Oligonucleotides of a defined sequence are synthesized on an amine-functionalized glass support. An amine function was attached at discrete locations on the glass slide using a solution of 700 ~~H~~ $\underline{\mu l}$ of $H_2N(CH_2)_3$ $Si(OCH_2CH_3)_3$ in 10 ml of 95% ethanol at room temperature for 3 hours. The treated support is washed once with methanol and then once with ethyl ether. The support was dried at room temperature and then baked at 110 °C for 15 hours. It was then washed with water, methanol and water, and then dried.

Please replace the paragraph beginning at page 173, line 8, with the following amended paragraph:

2. Method B: To the stirred mixture of 3-hydroxy benzophenone (1 g, 5 mM), anhydrous K_2CO_3 (3g, 23 mM) and NaI (500 mg) in dry acetone (40mL) was added 2-bromoethoxytetrahydropyran (1g, 5 mM) dissolved in 10 mL of dry acetone and refluxed for 20 h. The precipitate was filtered and washed with acetone (3x20 mL). The combined filtrate was evaporated and the yellowish residue obtained was purified by silica gel column chromatography using hexane/EtOAc (9:1) mixture as an eluent. Yield: 55- 60%. ^{1}H-NMR (500 MHz, $CDCl_3$) [[ä]] $\underline{\delta}$ ppm: 1.5-1.63 (m, 4H), 1.72 (m, 1H), 1.82 (m, 1H), 3.52 (m, 1H), 3.8-3.9 (m, 2H), 4.07 (m, 1H), 4.21 (m, 2H), 4.70(t, 1H), 7.15 (d, 1H), 7.37(m, 3H), (7.47 (t, 2H), 7.58(t,1H), 7.80(d,1H). Mass: 327.2(M^+), 349.3 ($M+Na^+$).

Please replace the paragraph beginning at page 173, line 8, with the following amended paragraph:

To a 100 mL two necked round-bottomed flask fitted with reflux condenser was placed activated Mg turnings (720 mg, 30 mM), a few crystals of I_2 and molecular ~~sileves~~ <u>sieves</u> (A4) under argon. To this mixture 10 ml of THF was added. The mixture was heated to 50°C and 2-(4-bromophenyl)-4,4-dimethyl-1,3-oxazoline (6.5g, 26 mM) dissolved in 15 mL of dry THF, a catalytic amount of CH_3I, RED-Al and CCl_4 were added with stirring and refluxed for 3h. After that the reaction mixture was cooled to room temperature and added phenyl-{3-[2-(tetrahydropyran-2-yloxy)-ethoxy]-phenyl}-methanone (5.1 g, 15.6 mM) dissolved in 15 mL of dry THF and again refluxed for 3 h, cooled and 3mL of water added. The solvent was removed

under ~~roraevaporator~~ rotaevaporator and extracted with $CHCl_3$ (3x100 mL) and dried over anhydrous Na_2SO_4. The residue obtained on removal of the solvent was separated by silica gel column chromatography using hexane/EtOAc (7:3) as an eluent. Evaporation of the column fraction yielded 2-{4'-(3-(2-tetrahydropyran-2-yloxy)ethoxy)phenyl-4"-phenyl)}-4,4-dimethyl-1,3-oxazoline (3) as a yellow crystalline solid (1.4g, 18%). ^{1}H-NMR(500 MHz, $CDCl_3$) [[ä]] δ ppm: 1.37 (s, 6H), 1.5-1.63 (m, 4H), 1.68 (m, 1H), 1.80(m, 1H), 2.85 (s, 1H, -OH), 3.49 (m, 1H), 3.75(m, 1H), 3.85(m, 1H), 3.97 (m, 1H), 4.09(m, 4H), 4.66 (t, 1H), 6.80(d, 1H), 6.84(d, 1H), 6.88(s,1H), 7.18-7.31(m, 6H), 7.34 (d, 2H), 7.87(d, 2H). Mass: 502.6 (M+1), 524.5 (M+Na$^+$).

Please replace the paragraph beginning at page 175, line 11, with the following amended paragraph:

2. **Method B**: To a stirred solution of trityl acid **5** (12 mg, 0.03 mM) in dry THF (4 mL) was added dicyclohexyl carbodiimide (DDC, 10 mg, 0.05 mM). The reaction mixture was stirred for 30 min at r.t., N-hydroxysuccinimide (11.5 mg, 0.1 mM) and a catalytic amount of DMAP was added and allowed to stir for overnight. The solvent was removed under rotaevaporator and the solid obtained was dissolved in dry ether. The precipitated DCU was filtered and the solvent ether was evaporated. The crude solid obtained was purified by preparative TLC plate. Yield 7 mg (50%). ^{1}H-NMR (500 MHz, $CDCl_3$) [[ä]] δ ppm : 2.90 (s, 4H), 3.92(t, 4H), 4.02 (t, 4H), 6.83(m, 2H), 7.25 (m, 3H), 7.34 (m, 4H), 7.50(d, 2H), 8.0(d, 2H).

Please replace the paragraph beginning at page 176, line 12, with the following amended paragraph:

To a stirred solution of trityl acid **8** (200 mg, 0.42 mM) in dry THF (6 mL) was added dicyclohexyl carbodiimide (DDC, 206mg, 1 mM). The reaction mixture was stirred for 30 min at r.t., and N-hydroxysuccinimide (70 mg, 0.6 mM) and a catalytic amount of DMAP added and was allowed to stir for overnight. The solvent was removed under rotaevaporator and the solid obtained was dissolved in dry ether. The precipitated DCU was filtered and the solvent ether was evaporated. The crude solid obtained was separated by silica column chromatography using CH_2Cl_2. Yield: about 120 mg. ^{1}H-NMR (500 MHz, $CDCl_3$) [[ä]] δ ppm : 1.70 (m, 2H), 1.9 (t, 2H), 2.9 (s, 4H), 3.5(m, 2H), 3.9 (t, 2H), 4.0(t, 2H), 6.85(m, 4H), 7.25 (m, 4H), 7.32 (m, 5H), 7.51(m, 3H), 8.09(d, 2H).

Please replace the paragraph beginning at page 176, line 25 with the following amended paragraph:

To a stirred solution of trityl acid **8** (280 mg, 0.42 mM) in dry THF (6 mL) was added dicyclohexyl carbodiimide (DDC, 400mg, 1.95mM). The reaction mixture was stirred for 30 min at r.t., and maleimide (100 mg, 1.1 mM) and a catalytic amount of DMAP was added and allowed to stir for overnight. The solvent was removed under rotaevaporator and the solid obtained was dissolved in dry ether. The precipitated DCU was filtered and the solvent ether was evaporated. Part of the product was purified by preparative TLC. Yield: 12 mg. ^{1}H-NMR (500 MHz, $CDCl_3$) [[ä]] <u>δ</u> ppm : 1.78 (m, 2H), 1.95 (m 2H), 2.9 (s, 4H), 3.51(m, 2H), 3.93(t, 2H), 4.02(t, 2H), 6.8(m, 5H), 7.25 (m, 5H), 7.29 (m, 5H), 7.37(m, 3H), 7.48(d, 2H) , Mass: 561.3 (M^+).

Please replace the paragraph beginning at page 177, line 6, with the following amended paragraph:

This Example shows addition of a selectivity function onto a capture compound possessing a N-hydroxy succinimidyl ester reactivity function. Compounds with <u>a</u> sorting <u>function</u> can be prepared by using an appropriate analog of compound 11 below.

Please replace the paragraph beginning at page 180, line 2, with the following amended paragraph:

General Procedure: A solution of 4-(diphenylhydroxymethyl)benzoic acid (0.04 mM) in 1 mL of $SOCl_2$ was refluxed for 1 h and the excess $SOCl_2$ was removed under high vacuum. To this yellow solid residue obtained was added maleimide (0.045 mM) dissolved in dry freshly distilled THF (1 mL) and stirred at room temperature for 2h. The solvent was removed and added the corresponding alcohol (ROH, 2-5 fold excess) dissolved in dry pyridine (1mL) with stirring. After the reaction mixture stirred at room temperature for overnight the solution was extracted with CH_2Cl_2 (5x3mL) and dried over anhydrous Na_2SO_4. The residue obtained on evaporation of the solvent was separated by preparative TLC (Silica Gel, 500 ~~ìm~~ <u>µm</u> plate) and gave the product 1 in 50-60% yield. The trityl derivatives 1 were fully characterized by ^{1}H NMR and mass spectral data.

Please replace the paragraph beginning at page 185, line 3, with the following amended paragraph:

This example shows exemplary capture binding assays and the effects of selectivity functions on binding. This example shows that changing selectivity can alter reactivity of the capture compound thereby providing a means to probe biomolecule structures and to permit sorting or diversity reduction using the collections. In this example, the core group of the capture compounds is a trityl group and the reactive group is succinimide, which interacts with a primary amine. Compound 1341 is a non-selective compound that has a reactivity group, but no selectivity group. Compound 1343 (see Figure 20) is exemplary of such compound where the selectivity ~~goup~~ group is -OH. As the selectivity group changes there is a difference in reactivity on the target proteins (lysozyme, cytochrome C and ubiquitin).

Please replace the paragraph beginning at page 185, line 15, with the following amended paragraph:

Three different capture compounds (designated HKC 1343, 1349, 1365; chemical structure of each compound is listed below the Compound name) were reacted individually with Lysozyme (Accession number P00698; Figure 20b). The capture experiments were analyzed using MALDI-TOF Mass Spectrometry. Binding was performed in 20 ~~uL~~ μL sample volumes with a 5 ~~uM~~ μM Lysozyme concentrations in 25 mM HEPES buffer solution, pH 7.0. The trityl-based capture compounds were added to the protein solution at a 10 ~~uM~~ μM concentration. The binding reaction was incubated at room temperature for 30 minutes. The reaction was quenched using 1 ~~uL~~ μL of a 100 mM TRIZMA base solution.

Please replace the paragraph beginning at page 185, line 25, with the following amended paragraph:

The capture compound-protein binding mixture was prepared for mass spectrometry by mixing a 1 ~~uL~~ μL aliquot of a binding reaction with 1 ~~uL~~ μL of a 10mg/mL sinapinic acid in 30% aqueous acetonitrile. The sample was deposited as a 500 nL spot on the surface of the mass target plates and air-dried before mass spectrometric analysis. The results of the mass spectrometry analysis, which are shown in Figure 20b, demonstrate that addition of selectivity groups to compounds permits alterations in the binding specificity of capture compounds.

Please replace the paragraph beginning at page 186, line 3, with the following amended paragraph:

Four different capture compounds (designated HKC 1341, 1343, 1349, 1365; chemical structure of each compound is listed below the Compound name) were reacted individually with Cytochrome C (accession number: P00006, Figure 20c). The capture experiments were analyzed using MALDI-TOF Mass Spectrometry. Binding was performed in 20 ~~uL~~ μL sample volumes with a 5 ~~uM~~ μM Cytochrome C concentrations in 25 mM HEPES buffer solution, pH 7.0. The trityl-based capture compounds were added to the protein solution at a 10 ~~uM~~ μM concentration. The binding reaction was incubated at room temperature for 30 minutes. The reaction was quenched using 1 ~~uL~~ μL of a 100 mM TRIZMA base solution. The capture compound-protein binding mixture was prepared for mass spectrometry analysis by mixing a 1 ~~uL~~ μL aliquot of the binding reaction with 1 ~~uL~~ μL of a 10mg/mL sinapinic acid in 30% aqueous acetonitrile. The sample was deposited as a 500 nL spot on the surface of mass target plates and subsequently air-dried before mass spectrometric analyses. The results of the mass spectrometry analysis, which shown in Figure 20c, demonstrate that addition of selectivity groups to compounds permits alterations in the binding specificity of capture compounds.

Please replace the paragraph beginning at page 186, line 21, with the following amended paragraph:

One of the exemplary capture compounds (HKC 1343) was incubated with a mixture of three different proteins (Ubiquitin, [P02248], Cytochrome C [P00006] and Lysozyme [P00698]) (see, Figure 20d). The capture experiment was analyzed using MALDI-TOF Mass Spectrometry. The binding reactions were performed in a 20 ~~uL~~ μL sample volume with all three proteins at 5 ~~uM~~ μM concentrations in 25 mM HEPES buffer solution pH 7.0. The trityl-based capture compound was added to the protein solution at a 25 ~~uM~~ μM concentration. The binding reaction was incubated at room temperature for 30 minutes and the reaction quenched using 1 ~~uL~~ μL of a 100 mM TRIZMA base solution. The capture compound-protein binding mixture was prepared for mass spectrometry by mixing a 1 uL aliquot of the binding reaction with 1 ~~uL~~ μL of 10mg/mL sinapinic acid in 30% aqueous acetonitrile. The sample was deposited as a 500 nL spot on the surface of mass target plates and air-dried before mass spectral analysis. The results of the mass

spectrometry analysis, which are shown in Figure 20d, demonstrate that a plurality of compounds bound to a single capture agent that is selective can be identified by mass spectrometric analysis.

Please replace the paragraph beginning at page 187, line 8, with the following amended paragraph:

Another of the exemplary capture compounds (HKC 1365) was incubated with a mixture of three different proteins (Ubiquitin [P02248], Cytochrome C [P00006] and Lysozyme [P00698]; see Figure 20d). The capture experiment was analyzed using MALDI-TOF Mass Spectrometry. The binding reactions were performed in a 20 ~~uL~~ μL sample volume with all three proteins at 5 ~~uM~~ μM concentrations in 25 mM HEPES buffer solution pH 7.0. The trityl-based capture compound was added to the protein solution at a 15 ~~uM~~ μM concentration. The binding reaction was incubated at room temperature for 30 minutes, and quenched using 1 ~~uL~~ μL of a 100 mM TRIZMA base solution. The capture compound-protein binding mixture was prepared for mass spectrometry by mixing a 1 ~~uL~~ μL aliquot of the binding reaction with 1 ~~uL~~ μL of a 10mg/mL sinapinic acid in 30% aqueous acetonitrile. The sample was deposited as a 500 nL spot on the surface of the mass target plates and air-dried before mass spectral analyses. The results of the mass spectrometry analysis, which are shown in Figure 20e, demonstrate that a plurality of compounds bound to a single capture agent that is selective can be identified by mass spectrometric analysis.

Please replace the paragraph beginning at page 188, line 13, with the following amended paragraph:

A protein dilution (mixture) is prepared in the reaction buffer at the concentration of 0.5, 2.5 and 3 ~~ìM~~ μM, for ubiquitin, cytochrome c and lysozyme, respectively. 19.5 ~~ìl~~ μl is used for one capturing reaction. Each reaction is started by adding 0.5 ~~ìl~~ μl of 1 mM compound stock solution (final 25 ~~ìM~~ μM). The reaction mixture is incubated at room temperature for 30 min before the reaction is stopped by the addition of 5 mM TRIZMA.

Please replace the paragraph beginning at page 188, line 19, with the following amended paragraph:

Three different reactions are run. The first two tubes contain HKC 1343 and HKC 1365 individually, and a third one is started by adding compounds HKC 1343 and 1365 (final

concentration 25 ~~iM~~ μM for each compound). After the reaction, 1 ~~il~~ μl of each sample is mixed with equal volume of matrix and subjected to MALDI analysis. Statistic significance of the results is ensured by triplicate each reaction sample.

Please replace the paragraph beginning at page 190, line 11, with the following amended paragraph:

To a solution of powdered KOH (45 mg, 0.8 mM) in anhydrous DMSO (2.5 mL) at room temperature was added 3-{[4-(4,4-Dimethyl-4,5-dihydro-oxazol-2-yl)-phenyl]-hydroxy-phenyl-methyl}-phenol (**2**, 150 mg, 0.4 mM) and (3-Bromo-propyl)-carbamic acid tert-butyl ester (96 mg, 0.4 mM). The reaction mixture was stirred at room temperature for 3h. Then the reaction mixture was extracted with ethyl acetate (3x25 mL) and the ~~combin-ed~~ combined extract was dried over anhydrous Mg_2SO_4. The residue obtained on evaporation of the solvent was purified by silica gel chromatography using hexane/EtOAc (1:1) as an eluent. ~~Evapoartion~~ Evaporation of the solvent gave **3**. Yield: >220 mg (quantitative yield). Mass: 531 (MH+).

Please replace the paragraph beginning at page 191, line 6, with the following amended paragraph:

A mixture of Trityl amino acid (4, 100 mg, 0.26 mM) and Biotin-X-NHS (113mg, 0.25 mM) was stirred at room temperature in 3 mL of anhydrous DMF for overnight. After that DMF was removed under high vacuum and the residue obtained was passed through silica gel column using 50% $CH_3OH/CHCl_3$ as a solvent. Evaporation of the solvent ~~yieded biotinlated~~ yielded biotinylated trityl acid 5. (97.8%). Mass: 739(M Na+) , 715 (M-H).

Please replace the paragraph beginning at page 192, line 19, with the following amended paragraph:

This example shows addition of ~~of~~ a biotin as a sorting function onto a capture compound.

Please replace the paragraph beginning at page 194, line 11, with the following amended paragraph:

Pierce spin columns (about 500 ~~ul~~ μl bed volume). It handles as little as 20 μl and up to 100 μl sample.

Please replace the paragraph beginning at page 194, line 25, with the following amended paragraph:

A. In a well on a reaction plate, ~~pipett~~ pipette 25 µl FT293, x µl of Carbonic Anhydrase II stock, y µl of compound stock solution, and 25-x-y µl of 20 mM Hepes buffer, pH 7.2. Keep the y value at 2.5 ~~ul~~ µl or less for a 50 ~~ul~~ µl reaction. The FT fraction in the mixture is diluted 2 fold in the final mixture. For S100, more than 3-fold dilution is required. In certain embodiments, use 15 ~~ul~~ µl for S100 in a 50 ~~ul~~ µl reaction and change the buffer volume accordingly.

Please replace the paragraph beginning at page 195, line 7, with the following amended paragraph:

E. Spin column processing of sample after photoreaction is not necessary for mixture that has the capture compound around 1 uM. For reactions using more than 10 ~~uM~~ µM compound, spin-column processing before binding can improve the target signal in pull-down.

Please replace the paragraph beginning at page 195, line 11, with the following amended paragraph:

F. Isolate captured protein using biotin/avidin. [[.]] Wash Soft-Link resin as above; do not pre-treat with biotin. For each binding and pull-down, into one PCR tube on a strip, add 5 ~~ul~~ µl slurry of resin after mixing the resin and the liquid on top thoroughly, then add 20 ~~ul~~ µl reaction mixture after photoreaction or after spin-column. Care should be taken to make sure that the tip is at the bottom of the tube before releasing the contents, and the ~~pipettman~~ pipette tips should not touch the inside wall of the tube, especially the top part. Rotate the binding tube for 30 min at room temperature.

Please replace the paragraph beginning at page 195, line 22, with the following amended paragraph:

H. Add 200 ~~ul~~ µl washing buffer into each tube, rotate for 4 min on the same setting. Make sure the resins and liquid are well mixed during the process.

Please replace the paragraph beginning at page 195, line 26, with the following amended paragraph:

J. Following 4x washes by the washing buffer, switch to water, carry out another 4x washes. After the last wash in water, completely take out the supernatant, add 2 ~~ul~~ μl water on top.

Please replace the paragraph beginning at page 195, line 29, with the following amended paragraph:

K. Mix the resin and water well, take 1 ~~ul~~ μl onto a mass plate spot, give 1 or 2 minute to air dry the spot a bit (not completely dry), add 1 ~~ul~~ μl of matrix, ~~pipett~~ pipette up and down 4 times.

Please replace the paragraph beginning at page 196, line 7, with the following amended paragraph:

~~this~~ This approach is based on the observation that photolysis acts on a very fast time scale, from activation to covalent cross linking (ns to ms, depending on the photoactive moiety). One can thus envision using photolysis to take a snap shot of a enzyme-substrate complex mixture in equilibrium. The amount of covalently crosslinked enzyme-substrate is directly proportional to that of the enzyme-bound substrate (capture compound) in equilibrium. Most importantly, this ~~amout~~ amount as a fraction of that of the starting enzyme can be very easily and reliably measured by using an off-the-shelf ~~Maldi~~ MALDI Machine following a pulldown step.

Please replace the paragraph beginning at page 198, line 7, with the following amended paragraph:

Thus by plotting the natural log of the relative areas against $1/[S_0]$, the difference in dissociation ~~contants~~ constants, $(K_d^1 - K_d^2)$ can be determined directly from the slope of the linear fit. The appealing feature of this analysis is that since we are dealing with relative areas, there is no need to normalize the areas from different spectra.

Please replace the paragraph beginning at page 198, line 12, with the following amended paragraph:

EXAMPLE 16 ~~(PROPHETIC)~~

Please replace the paragraph beginning at page 200, line 16, with the following amended paragraph:

- Glitazone-treated ~~treat~~ patients may experience weight gains in the range of 1 to 4 kg may occur perhaps improved due to glucose control. The glitazones are reported to produce increases in low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), and total cholesterol. LDL-C is increased the least with pioglitazone. The LDL/HDL ratio is preserved, although with rosiglitazone, there is a lag time of several months before HDL-C rises relative to LDL-C. Triglycerides decrease with troglitazone and pioglitazone, whereas the effect with rosiglitazone is variable.

Please replace the paragraph beginning at page 202, line 8 with the following amended paragraph:

- Pharmacokinetic-based interactions: Interference with Absorption, Metabolism/~~Cytochromebased~~ Cytochrome-based interactions, Competition for elimination, etc.